Low CD4 Count Is Associated With an Increased Risk of Fragility Fracture in HIV-Infected Patients

Michelle K. Yong, MBBS, FRACP, MPH, Julian H. Elliott, MBBS, FRACP, PhD,*†‡*
Ian J. Woolley, MBBS, FRACP, DTMH,‡ and Jennifer F. Hoy, MBBS, FRACP*‡*

Background: Low bone mineral density in HIV-infected patients is an increasingly recognized clinical problem. The aim of this study was to determine the incidence, prevalence, and risk factors for development of low trauma or fragility fractures in an HIV-infected population.

Methods: A 1:2 matched case–control study was performed of HIV-infected patients attending the Alfred Hospital between 1998 and 2009. Controls were matched on gender, age, and duration of HIV infection.

Results: The overall fracture incidence rate was 0.53 per 100 person-years [95% confidence interval (CI): 0.43 to 0.65] and period prevalence of 3.34 per 100 patients (95% CI: 2.66 to 4.13). There were 73 low trauma fractures in 61 patients. Patients were predominantly male (89%) with a mean age of 49.8 years. Independent risk factors for fragility fracture were a CD4 cell count $<$200 cells per microliter odds ratio (OR): 4.91 (95% CI: 1.78 to 13.57, $P = 0.002$), corticosteroids OR: 8.96 (95% CI: 1.55 to 51.88, $P = 0.014$) and anti-epileptic medications OR: 8.88 (95% CI: 1.75 to 44.97, $P = 0.008$). There were no significant associations between HIV viremia ($P = 0.18$), use of or class of antiretroviral medication, and risk of fracture. Eighty-eight percent of patients with fracture had established osteopenia or osteoporosis.

Conclusion: This is the largest clinical study to date of fragility fractures occurring in an HIV-infected population. The study found that risk of fracture was strongly associated with a low CD4 cell count, use of corticosteroids, and anti-epileptic medications. There were no associations between fracture risk and viral load, use of class, or duration of antiretroviral agent.

Key Words: CD4, fracture, HIV, osteoporosis, osteopenia

(*J Acquir Immune Defic Syndr* 2011;57:205–210)

BACKGROUND

Bone disease in HIV-infected patients is an increasingly recognized clinical problem with studies showing an increased prevalence of osteopenia, osteoporosis, and fragility fractures compared with the non-HIV population.[1–7] As the number of people living with well-controlled HIV increases, they will be at risk of developing age-related illnesses such as osteoporosis and osteoporosis-related fractures. Despite the growing concern of osteopenia/osteoporosis, only a few published studies have examined the outcome of fragility fractures.[2,4,7–9] Of these, the number of clinical fractures has been small,[8,9] did not include HIV-specific parameters,[2,7] or did not differentiate between high trauma and fragility fractures.[2,8] Specific risk factors for development of fragility fracture in HIV-infected patients have not been well described.

Much interest has surrounded the role of antiretroviral agents and antiretroviral class on changes in bone mineral density. Recent literature suggests that patients are more likely to develop osteoporosis whilst on antiretroviral therapy as opposed to not on therapy.[5,10] The antiretroviral agents most closely implicated with accelerated bone loss include protease inhibitors, tenofovir, and efavirenz.[5,11] Other traditional osteoporosis risk factors such as smoking, family history, vitamin D deficiency, and lactic acidaemia are also common in HIV patients and likely to be contributory.[12]

Chronic immune activation and upregulation of inflammatory cytokines may play a role in the pathogenesis of bone mineral loss in HIV patients.[13] Osteoclast activity is stimulated by pro-inflammatory cytokines such as tumor necrosis factor and interleukins (eg, IL-6) both of which are produced in increased amounts in HIV patients.[14,15] Persistent cytokine dysfunction may occur despite viral suppression with highly active antiretroviral therapy,[16] which may explain the higher prevalence of bone demineralization seen in chronic HIV infection. Some medications have diverse immunomodulatory effect such as statins, which have been shown to decrease inflammatory markers and decrease bone resorption.[17] However, the exact role of statins on bone mineral density is still unclear. In the non–HIV-infected population, a number of clinical observational studies found a significantly reduced fracture risk in patients currently exposed to statins,[18–20] whereas other studies found no difference.[21]

The aim of this study was to determine the incidence and prevalence of fractures in our HIV population and to determine risk factors for development of low trauma or atraumatic fracture.

METHODS

The study population was that of adult (≥18 years) male or female HIV-infected patients attending The Alfred Hospital, Melbourne, Australia, between January 1998 to June 2009.

Received for publication December 16, 2010; accepted April 8, 2011.
From the *Department of Infectious Diseases, The Alfred Hospital, Melbourne, Australia; †Burnet Institute, Melbourne, Australia; and ‡Department of Medicine, Monash University, Melbourne, Australia.
The authors have no funding or conflicts of interest to disclose.
Correspondence to: Michelle K. Yong, MBBS, FRACP, MPH, Infectious Diseases Unit, The Alfred Hospital, 2nd floor, Burnet Institute, 85 Commercial Road, Melbourne, VIC 3004, Australia (e-mail: m.yong@alfred.org.au).

Fracture cases were identified through 1 of 2 sources: the Victorian HIV Database which records demographic and medical data, including co-morbidities on > 4300 patients utilizing the Victorian HIV Service; and The Alfred Hospital International Classification of Diseases (ICD) coding system to identify those patients who were admitted to The Alfred Hospital with a fracture. Fracture incidence rate was calculated by dividing the number of fractures by the period of risk for all included patients during the study period expressed as per 100 person-years of follow-up. Period prevalence was calculated as the number of patients with fractures per 100 persons during the same study period.

The medical records of each identified case were then individually reviewed by the investigator to verify details of the fracture such as date, site, and nature. A low traumatic fracture was defined as a fracture sustained from standing height or less. Data were collected on basic demographics, age, gender, ethnicity, height, weight, CD4 cell count, HIV viral load, medical comorbidities, concurrent medications, and dual X-ray absorptiometry (DEXA) scan results. Osteoporosis was defined by a DEXA *t* score of <2.5 SD and osteopenia by <1–2.5 SD below the norm mean value for young adults.[22]

Pharmacy charts and prescriptions were used to identify those on antiretroviral therapy, testosterone/oestrogen supplements, corticosteroid, anti-epileptic, proton pump inhibitor therapy, and statins. Controls were matched for gender, age (±5 years) and duration of known HIV infection (±2 years) and were selected from each successive consecutive HIV patient attending the hospital over a 2-month period who met eligibility.

Data were analyzed using conditional logistic regression to determine crude and adjusted odds ratio (OR). Only the first fracture episode per patient was included in the study analysis. A *P* value <0.05 was considered statistically significant. We compared continuous variables such as CD4 cell count and HIV viral load by Mann Whitney *U* test. The data were analyzed using Stata/SE 9.2 for Windows (College Station, TX). Ethics was approved by the Human Research Ethics Committee of The Alfred Hospital and Monash University.

RESULTS

Overall, there were 94 documented fractures sustained in 81 HIV-infected patients. A total of 2424 patients contributed to 17,622 patient follow-up years, therefore providing a fracture incidence rate of 0.53 per 100 person-years follow-up (95% CI: 0.43 to 0.65 per 100 person-years follow-up) or period prevalence of 3.34 per 100 patients (95% CI: 2.66 to 4.13 per 100 patients). Twenty-one fractures were excluded as a result of high trauma mechanisms (mainly motor vehicle accidents or assaults) and were excluded from further analysis, leaving 73 atraumatic or low trauma fractures in 61 HIV-infected patients.

The mean age at the time of the fracture was 49.8 years (Table 1). More than half (58%) of the fractures occurred in patients younger than 50 years including 20%, which occurred within the youngest age category of <39 years. Patients were predominantly male (89%), of white background (92%), and had been infected with HIV for a median of 11.4 years, reflecting the HIV population receiving care at The Alfred Hospital. Although patients were not specifically matched for ethnicity, both cases and controls had similar ethnic backgrounds. The baseline demographics in both cases and controls were well matched.

The most common fracture sites were vertebral (25%), neck of femur (21%), and wrist (18%), which is very similar to the spectrum of fragility fractures seen in a non–HIV-infected osteoporotic population (Table 2). Patients with vertebral crush fractures commonly presented with back pain without prior history of trauma. Vertebral fractures often involved several vertebral levels with one patient having involvement of the second cervical vertebra (Hangman fracture). Lower limb fractures commonly presented after minimal trauma such as twisting of the ankle or fall from standing height. Ten patients went on to subsequently sustain another fracture with the majority (80%) occurring at a site different to the first fracture. Another 2 patients developed a third low trauma fracture.

Body mass index (BMI) data were available for 68.3% (125 of 183) of all study participants (Table 1). Of the 58 participants with missing BMI data, weight was not recorded in 20 (34%), height in 16 (28%), and both weight and height were not recorded in 22 (38%) patients. Control patients had a higher BMI compared with cases (25.2 vs. 22.5 $P = 0.001$). More HIV patients with fractures were observed to be underweight, defined as a BMI <20 kg/m^2, compared with controls (27% vs. 11%), However, being underweight did not significantly increase the risk of fracture compared with normal weight (OR: 1.81, 95% CI: 0.56 to 5.8, $P = 0.32$). More obese patients were observed in the control group than cases (14% vs. 6%), but this was not significantly protective for risk of fracture compared with normal weight (OR: 0.22, 95% CI: 0.02 to 1.95, $P = 0.17$) BMI was not significantly associated with risk of fracture, although data were not available for one-third of all patients.

The median CD4 cell count in fracture patients was significantly lower compared with controls (283 cells/μL vs. 448 cells/μL $P = 0.0003$). In univariate analysis, patients with a CD4 cell count of less than <200 cells per microliter were 6.7 times more likely to have a fracture (OR: 6.77, 95% CI: 2.4 to 19.1, $P < 0.001$) when compared with those with a CD4 cell count of >500 cells per microliter (Table 1). The increased risk of fracture was also significant in patients with a CD4 cell count in the range of 200–500 cells/μL (OR: 2.1, 95% CI: 1.06 to 5.44, $P = 0.036$). No significant difference was observed between the median HIV viral load of cases and controls (118 copies/mL vs. 50 copies/mL $P = 0.07$). There was no difference in fracture risk between patients who had a detectable viral load >400 copies per milliliter compared with suppressed viral load <400 copies per milliliter (OR: 1.69, 95% CI: 0.97 to 1.32, $P = 0.18$). Of the patients who had a viral load <400 copies per milliliter at the index date, the duration of preceding virological suppression was not significantly associated with fracture (OR: 0.96 $P = 0.69$).

Bone densitometry scans (DEXA) were available for 34 (56%) of fracture cases and 36 (30%) of controls. Of HIV-infected patients with low trauma fractures and available DEXA scan, 88% had established low bone mineral density (BMD), with osteopenia (32%) or osteoporosis (56%). Having osteoporosis significantly increased the risk of fracture, OR: 46.9 (95% CI: 2.52 to 872, $P < 0.01$). For control patients without known

TABLE 1. Demographic and HIV Characteristics of Case and Control Patients

Characteristics	Case Patients, n = 61 (%)	Control Patients, n = 122 (%)	Odds ratio, (95% CI)	*P*	Multivariate, OR (95% CI)	*P*
Age (mean)	49.8	49.5	—	—	—	—
<39	12 (20)	19 (16)	—	—	—	—
40–49	23 (38)	54 (44)	—	—	—	—
50–59	13 (21)	24 (20)	—	—	—	—
>60	13 (21)	25 (21)	—	—	—	—
Sex						
Men	54 (89)	108 (89)	—	—	—	—
Women	7 (11)	14 (11)	—	—	—	—
Ethnicity						
White	56 (92)	113 (93)	—	—	—	—
Black	2 (3)	5 (4)	—	—	—	—
Asian	3 (5)	4 (3)	—	—	—	—
Duration of HIV (yrs)	11.4	11.2	—	—	—	—
Route of infection						
Sexual exposure	47 (77)	102 (84)	—	—	—	—
Blood transfusion	5 (8)	5 (4)	—	—	—	—
Injecting drug use	1 (2)	3 (2)	—	—	—	—
Unknown	8 (13)	12 (10)	—	—	—	—
Chronic hepatitis B	3 (5)	15 (12)	0.38 (0.12 to 1.35)	0.14	—	—
Chronic hepatitis C	16 (26)	30 (25)	1.22 (0.55 to 2.71)	0.63	—	—
Previous opportunistic infection	37 (60)	45 (37)	3.26 (1.54 to 6.89)	0.002	—	—
Mean nadir CD4 count (cells/μL)	102	151	0.99 (0.99 to 1.0)	0.01	—	—
BMI, kg/m^2						
<20 Underweight	13 (27)	8 (11)	1.81 (0.56 to 5.8)	0.32	—	—
20.1–25 Normal	20 (41)	33 (43)	1.00	—	—	—
25.1–30 Overweight	13 (26)	24 (32)	0.74 (0.3 to 1.87)	0.53	—	—
>30.1 Obese	3 (6)	11 (14)	0.22 (0.02–1.95)	0.17	—	—
Unknown	12	46	—	—	—	—
Mean BMI	22.5	25.2	—	0.001		
Median CD4 cell count (cells/μL)	283	448	—	0.0003	—	—
Absolute CD4 cell count (cells/μL)						
<200	21 (36)	16 (14)	6.77 (2.4 to 19.1)	<0.001	4.91 (1.78 to 13.57)	0.002
200–500	27 (46)	46 (41)	2.4 (1.06 to 5.44)	0.036	—	—
>500	11 (19)	50 (45)	1.00	—	—	—
Median HIV viral load (copies/mL)	118	50	—	0.07	—	—
Absolute HIV viral load (copies/mL)						
<400	37 (64)	80 (73)	1.00	—	—	—
>400	21 (36)	30 (27)	1.69 (0.97–1.32)	0.18	—	—
Duration of viral suppression (yrs)*	5.58	2.97	0.96 (0.81 to 1.15)	0.69	—	—
DEXA Scan performed	34	36	—	—	—	—
Normal	4 (12)	16 (44)	1.00	—	—	—
Osteopenia (t score < 1–2.5 SD)	11 (32)	16 (44)	4.60 (0.51 to 41.3)	0.17	—	—
Osteoporosis (t score < 2.5 SD)	19 (56)	4 (11)	46.9 (2.52 to 872)	<0.01	—	—

*Applicable to patients who have <400 copies per milliliter viral load at the index date.

fractures, more than half had established osteopenia (44%) or osteoporosis (11%). There were insufficient DEXA scan results to be able to analyze DEXA outcome with BMI, CD4 cell count, HIV viral load, and concurrent medications.

There was no significant association between fracture risk and current use of antiretroviral agent (OR: 1.0) compared with no treatment (Table 3). In univariate analysis, a longer duration of nonnucleoside reverse transcriptase inhibitor exposure nearly reached significance for being protective against fracture ($P = 0.06$), but this was non significant on multivariate analysis. Fracture risk was analyzed for any association between use and/or duration of a nucleoside reverse transcriptase inhibitor (tenofovir), protease inhibitors, and non-nucleoside reverse transcriptase inhibitors. There were no significant associations seen between fracture risk and any of the antiretroviral classes.

TABLE 2. Fracture Site in Order of Frequency

Fracture Site (n = 73)	n (%)
Vertebral	18 (25)
Neck of Femur	15 (21)
Wrist (Colles)	13 (18)
Ankle	8 (11)
Foot	8 (11)
Humerus	6 (8)
Ribs	5 (7)

There was a statistically significant association between risk of fracture and concurrent corticosteroid use (multivariate OR: 8.96, 95% CI: 1.55 to 51.88, $P = 0.014$). Steroid therapy was commonly prescribed as adjuvant therapy in treating HIV-specific illnesses; lymphoma/malignancy (n = 4), inflammatory arthritis (n = 3), immune reconstitution syndrome (n = 2) and aphthous mouth ulcers (n = 1). Increased risk of fracture was also observed with concurrent anti-epileptic medications (multivariate OR: 8.88 (95% CI: 1.75 to 44.97, $P = 0.008$), which were frequently prescribed for indications such as painful peripheral neuropathy (n = 6), mood disorders (n = 4), chronic pain syndrome (n = 2), and postherpetic neuralgia (n = 1) rather than a primary seizure disorder (n = 3). In unvariate analysis, a reduced risk of fracture was seen in patients taking statin therapy OR: 0.30 (95% CI: 0.10 to 0.94, $P < 0.04$) and an increased risk seen with proton pump inhibitors OR: 2.93 (95% CI: 1.20 to 7.15, $P < 0.02$), but these were both not significant on multivariate analysis. There were few patients on sex hormone replacement therapy such as testosterone, and this was not associated with fracture risk in this study.

In a multivariate analysis, the factors which remained independently associated with fracture risk were index CD4 cell count <200 cells per microliter, (OR: 4.91, 95% CI: 1.78 to 13.57, $P = 0.002$), steroid therapy (OR: 8.96, 95% CI: 1.55 to 51.88, $P = 0.014$), and anti-epileptic medications (OR: 8.88, 95% CI: 1.75 to 44.97, $P = 0.008$).

DISCUSSION

This study, of the largest series of fragility fractures occurring in HIV patients reported to date, found that a low CD4 count, but not high viral load, was strongly associated with an increased risk of fracture. Patients with a CD4 cell count <200 cells per microliter had an almost 5 times increased risk of developing a fragility fracture that was not dependent on the known duration of HIV infection as this factor was controlled for in the study design. Systemic corticosteroids and anti-epileptic medications were also associated with an increased risk of fracture, but use of duration or class of antiretroviral agent was not.

The fracture incidence rate in this study of 0.53 per 100 person-years follow-up is comparable with that reported by Collin et al.[8] Likewise, the prevalence of 3.87 per 100 patients is similar to the US population based study by Triant et al,[2] which found an increased prevalence of fractures in HIV patients (2.87 per 100 patients) compared with non-HIV patients (1.77 per 100 patients). Although Triant et al described the significance of fractures in an HIV population, individual clinical information was not obtained such as the presence of osteoporosis/osteopenia, exclusion of high impact trauma cases, or HIV-related information such as CD4 markers or antiretroviral medications. Other published studies also lacked individual clinical data,[9] included traumatic fractures,[8] were in a select group of patients,[7] or lacked a control population.[4]

This study is the first to report an association between low CD4 cell count and increased risk of fragility fracture. Current literature has not associated CD4 cell count to fracture risk,[23] although an association with nadir CD4 cell count and development of osteoporosis/osteopenia has previously been reported.[24,25] One possible mechanism may be that patients with poor immunological recovery have persistently upregulated proinflammatory cytokines making them susceptible to fracture.[14] Dysregulated bone metabolism has also been seen in patients with advanced HIV disease.[14] This study did not

TABLE 3. Medication Use at Time of Fracture of Case and Control Patients

Medication	Case, n = 61 (%)	Control, n = 122 (%)	Univariate, OR (95% CI)	P	Multivariate, OR (95% CI)	*P*
Antiretroviral agent (yes/no)						
Tenofovir	19 (31)	40 (33)	0.91 (0.43 to 1.90)	0.80	—	—
Protease inhibitors	30 (49)	57 (47)	1.12 (0.58 to 2.16)	0.74	—	—
NNRTIs	20 (33)	49 (40)	0.72 (0.37 to 1.40)	0.33	—	—
No ARVs	10 (16)	20 (16)	1.00 (0.40 to 2.5)	1.0	—	—
Antiretroviral agent (mean duration/years)						
Tenofovir	1.55	1.93	0.89 (0.66 to 1.21)	0.48	—	—
Protease inhibitors	1.81	1.91	1.0 (0.77 to 1.29)	1.00	—	—
NNRTIs	2.45	3.49	0.85 (0.71 to 1.01)	0.06	—	—
Anti-epileptics	11 (18)	5 (4)	6.4 (1.76 to 23.3)	0.005	8.88 (1.75 to 44.97)	0.008
Systemic corticosteroids	8 (13)	2 (2)	8.00 (1.70 to 37.7)	0.01	8.96 (1.55 to 51.88)	0.014
Statin	7 (11)	28 (23)	0.30 (0.10 to 0.94)	0.04	—	—
Sex hormone replacement	3 (5)	1 (1)	6.0 (0.62 to 57.7)	0.12	—	—
Proton Pump inhibitors	13 (21)	10 (8)	2.93 (1.20 to 7.15)	0.02	—	—

NNRTI, nonnucleoside reverse transcriptase inhibitor.

demonstrate a corresponding increased risk of fracture with detectable viral load >400 copies per milliliter suggesting that those at risk are not necessarily the same as those with untreated/poorly controlled HIV infection. McComsey et al[4] reported a median CD4 cell count of 174 cells per milliliter (range: 7–908) at the time of fracture in their case series, but this was without a control comparison. Other studies of fractures in HIV infection did not collect HIV-specific markers such as CD4 cell count or viral load.[2,7,9] The association between low CD4 cell count and fracture risk suggest that chronic immune activation and persistent inflammation may play an important role in bone demineralization and fracture development.

In this study, no associations were found between fracture risk and antiretroviral therapy, either with use of, class or duration of antiretroviral agent. It is possible that there were too few cases to determine a true association with use of antiretroviral therapy and risk of fracture and a larger study is required. Controversy exists as to whether reduction in bone mineral density is related to HIV itself or to antiretroviral treatment, with a contribution from both likely. A meta-analysis performed on all studies reporting prevalence of reduced bone mineral density in HIV patients showed a significant increase in osteoporosis in those on antiretroviral therapy.[5] Exposure to protease inhibitors and tenofovir have been implicated in greater loss of bone mineral density.[11,26,27]

Corticosteroids are a potent cause of bone loss resulting in development of pathological fractures,[28] so it is not surprising that use of corticosteroids was associated with an increased risk of fragility fracture. It has been suggested that guidelines for monitoring and the use of prophylaxis be developed for corticosteroid induced osteoporosis,[29] given that steroids are commonly prescribed in HIV care for the management of opportunistic infections or malignancy. Anti-epileptic medications were also independently associated with an increased fracture risk in this study. Proposed mechanisms include altered hepatic enzymes and vitamin D dysregulation.[30] Caution should be taken with this observation as it is unknown how long patients were on therapy, and indications for treatment were largely for chronic neuropathic pain rather than a seizure disorder. Gabapentin rather than phenytoin or carbamazepine was more commonly prescribed. Vitamin D levels are unknown, but deficiency may be a significant confounder given that patients with chronic neuropathic pain may be more likely to remain indoors, with reduced mobility, and therefore be vitamin D deficient. Despite their diverse range of immunological effects, in this study, statins were not found to be associated with reduced fracture risk. A protective association of statins (OR: 0.30, $P = 0.04$), seen on univariate analysis, was no longer found to be significant on multivariate analysis.

More than half of the fractures in this study occurred in a relatively young group of patients younger than 50 years, implying that more fractures are likely to occur as this group ages. Increasing age is one of the strongest risk factors for development of fracture in the general population.[31] This was also observed in the study by Triant et al, where increasing fracture prevalence occurred particularly in those older than 40 years.[2] Patients who have had a prior fracture are also much more likely to sustain a further fracture.[32,33]

Although abnormal DEXA scans accurately confirmed the presence of osteopenia and osteoporosis in fracture cases, it was not performed in a large proportion of cases (44%). This finding was similar to a previous study where only 20% of patients with fractures underwent DEXA scanning,[4] suggesting a lack of appreciation or under investigation of bone disease by those managing HIV patients. DEXA-based *t* score definitions of osteoporosis and osteopenia are based on white older females. Applying *t* scores classifications to this group of predominantly younger male HIV-infected participants may not be suitable. Although *Z* scores are referenced to patients of a similar age and sex, the scores lack standardization and vary widely.[34] There were insufficient *Z* score results in this study to allow meaningful interpretation. The number of patients tested for vitamin D levels would also be of interest as this is a potential reversible contributor of low bone mineral density. There was a high prevalence (55%) of osteopenia or osteoporosis in the control group, which is in keeping with previously published studies.[24,35]

There are a number of limitations to our study including the retrospective nature of the study design. However, given the relatively infrequent number of clinical fractures observed, prospective studies would require a much longer study period. There was insufficient data available to assess important osteoporotic risk factors such as smoking, family history of fracture, alcohol consumption, and vitamin D levels. Not all subjects underwent DEXA scan measurement to be able to analyze the association of osteopenia or osteoporosis with CD4 cell count, HIV viral load, and concurrent medications. Lack of information on duration and dosage of medication was also a limitation.

In conclusion, bone demineralization and resultant fragility fractures are an emerging clinical problem affecting an increasingly aging HIV-infected population. Chronic inflammatory factors and antiretroviral treatment are thought to contribute to the pathogenesis of disease. This is the largest clinical study to date of fragility fractures occurring in an HIV-infected population. The study found that risk of fracture was independently associated with low CD4 cell count, use of corticosteroids, or anti-epileptic medications. There were no associations between fracture risk and use of class or duration of antiretroviral agent.

ACKNOWLEDGMENTS

We would like to acknowledge Stacey Aitchison and Emma Paige who kindly assisted in the collection of clinical data.

REFERENCES

1. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS*. 2000; 14:F63–F67.
2. Triant VA, Brown TT, Lee H, et al. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab*. 2008;93: 3499–3504.
3. Amorosa V, Tebas P. Bone disease and HIV infection. *Clin Infect Dis*. 2006;42:108–114.

4. McComsey GA, Huang JS, Woolley IJ, et al. Fragility fractures in HIV-infected patients: need for better understanding of diagnosis and management. *J Int Assoc Physicians AIDS Care (Chic Ill)*. 2004;3:86–91.
5. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. 2006;20: 2165–2174.
6. Bruera D, Luna N, David DO, et al. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. *AIDS*. 2003; 17:1917–1923.
7. Prior J, Burdge D, Maan E, et al. Fragility fractures and bone mineral density in HIV positive women: a case-control population-based study. *Osteoporos Int*. 2007;18:1345–1353.
8. Collin F, Duval X, Le Moing V, et al. Ten-year incidence and risk factors of bone fractures in a cohort of treated HIV1-infected adults. *AIDS*. 2009; 23:1021–1024.
9. Arnsten JH, Freeman R, Howard AA, et al. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. *AIDS*. 2007;21:617–623.
10. Grund B, Peng G, Gibert CL, et al. Continuous antiretroviral therapy decreases bone mineral density. *AIDS*. 2009;23:1519–1529.
11. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292:191–201.
12. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis*. 2010;51:937–946.
13. Thomas J, Doherty SM. HIV infection—a risk factor for osteoporosis. *J Acquir Immune Defic Syndr*. 2003;33:281–291.
14. Aukrust P, Haug CJ, Ueland T, et al. Decreased bone formative and enhanced resorptive markers in human immunodeficiency virus infection: indication of normalization of the bone-remodeling process during highly active antiretroviral therapy. *J Clin Endocrinol Metab*. 1999;84:145–150.
15. Lahdevirta J, Maury CP, Teppo AM, et al. Elevated levels of circulating cachectin/tumor necrosis factor in patients with acquired immunodeficiency syndrome. *Am J Med*. 1988;85:289–291.
16. Ledru E, Christeff N, Patey O, et al. Alteration of tumor necrosis factor-alpha T-cell homeostasis following potent antiretroviral therapy: contribution to the development of human immunodeficiency virus-associated lipodystrophy syndrome. *Blood*. 2000;95:3191–3198.
17. Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. *Science*. 1999;286:1946–1949.
18. Meier CR, Schlienger RG, Kraenzlin ME, et al. HMG-CoA reductase inhibitors and the risk of fractures. *JAMA*. 2000;283:3205–3210.
19. Wang PS, Solomon DH, Mogun H, et al. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA*. 2000;283:3211–326.
20. Rejnmark L, Olsen ML, Johnsen SP, et al. Hip fracture risk in statin users–a population-based Danish case-control study. *Osteoporos Int*. 2004;15: 452–458.
21. LaCroix AZ, Cauley JA, Pettinger M, et al. Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med*. 2003;139: 97–104.
22. Kanis, JA. *Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis*. Geneva, Switzerland: World Health Organization; 1994;4:368–381.
23. Fausto A, Bongiovanni M, Cicconi P, et al. Potential predictive factors of osteoporosis in HIV-positive subjects. *Bone*. 2006;38:893–897.
24. Cazanave C, Dupon M, Lavignolle-Aurillac V, et al. Reduced bone mineral density in HIV-infected patients: prevalence and associated factors. *AIDS*. 2008;22:395–402.
25. Brown TT, McComsey GA, King MS. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. *J Acquir Immune Defic Syndr*. 2009;51:554–561.
26. Castillo AB, Tarantal AF, Watnik MR, et al. Tenofovir treatment at 30 mg/kg/day can inhibit cortical bone mineralization in growing rhesus monkeys (Macaca mulatta). *J Orthop Res*. 2002;20:1185–1189.
27. Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. *Clin Infect Dis*. 2009;49:1591–1601.
28. Adler RA, Rosen CJ. Glucocorticoids and osteoporosis. *Endocrinol Metab Clin North Am*. 1994;23:641–654.
29. Panayotakopoulos GD, Day S, Peters BS, et al. Severe osteoporosis and multiple fractures in an AIDS patient treated with short-term steroids for lymphoma: a need for guidelines. *Int J STD AIDS*. 2006;17: 567–568.
30. Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. *Epilepsy Behav.* 2004;5(Suppl 2):S3–S15.
31. Kanis JA, Johnell O, Oden A, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int*. 2001;12:989–995.
32. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone.* 2004;35:375–382.
33. Center JR, Bliuc D, Nguyen TV, et al. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA*. 2007;297:387–394.
34. Carey JJ, Delaney MF, Love TE, et al. DXA-generated Z-scores and T-scores may differ substantially and significantly in young adults. *J Clin Densitom*. 2007;10:351–358.
35. Mondy K, Yarasheski K, Powderly WG, et al. Longitudinal evolution of bone mineral density and bone markers in human immunodeficiency virus-infected individuals. *Clin Infect Dis*. 2003;36:482–490.